On page 42 , the footnote to Table 2

A10

* RE = Relative Expression to the $(Gly_4Ser)_3$ SEQ ID NO: 3 clone

REMARKS

Claims 1-51 remain pending in the application.

Applicants elect Group I, claims 1-11 and 49 with traverse.

As for the election of species within Group I, applicants elect the species of the first domain being the immunoglobulin V_H and the species of the second domain being immunoglobulin V_L and the species of the repeated pattern being random or no exact sequence. The restriction requirement is traversed. Reconsideration of the restriction requirement is respectfully requested.

The Office Action asserts that the Groups are all separate and patentably distinct. However, the molecules in groups II and IV are members of the libraries of Groups I and III. Furthermore, the nucleic acid molecules merely encode the polypeptide molecules of the other groups. A search for any one of the Groups I-IV would inherently involve searching for the other Groups and therefore, there is no additional burden. Accordingly, applicants request that Groups I-IV be examined together.

As for the election of species, requiring and election of a species of linker is inappropriate and illogical considering the invention. The purpose of the invention is to randomize the linker size and nucleotide sequence to build a library of many different randomized linkers. There is no preferred linker until one selects many and compares the relative biological activity of each with attached domains.

As for the election of specific domains, it should be readily apparent to those reading the specification that many different domains could be used. While certain combinations may be preferred, the specific V_H and V_L will depend entirely on the patient

specific lymphoma. Accordingly, the election of species requirement should be withdrawn in its entirety.

CONCLUSIONS

It is submitted that the restriction is improper in part and that the election of species is improper in total. Withdrawal of the restriction requirement and substantive examination of claims 1-36, 44-45, 48 and 49 together, is respectfully requested.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No. 500933.

Respectfully submitted,

Date: April 30, 2003

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Marked up version of the specification

On page 15 first and second full paragraphs:

Figure 1 shows a Western blot analysis of scFv proteins generated in Example 1 in plant protoplasts. CJ is the scFv with the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker. The number of the lane refers to the # of the clone. The size in kilodaltons (kD) is shown on the left.

Figure 2 shows a Western blot analysis of scFv proteins generated in Example 2 in whole plants. CJ is the scFv with the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker. The number of the lane refers to the # of the clone. The size in kDa is shown on the left.

On page 23 first paragraph:

A linker that has been used to link Ig V_H and V_L domains into an scFv is the 15 amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO:3), commonly designated $(Gly_4Ser)_3$ SEQ ID NO: 3. A number of other linkers for scFv production have been described in Lawrence et al., *FEBS Letters*, 425: 479-484 (1998), Solar et al., *Protein Engineering*, 8:717-723 (1995), Alfthan et al, *Protein Engineering* 8: 725-731 (1995), Newton et al., *Biochemistry*, 35:545-553 (1996). Ager et al., *Human Gene Therapy*, 7: 2157-2164 (1996) and Koo et al., *Applied and Environmental Microbiology*, 64:2490-2496 (1998), The library approach of this invention will generate many useful linkers beyond those noted above.

On page 35, last paragraph bridging page 36:

The immunogenic scFv protein designated "CJ" was derived from human lymphoma patient (having the initials CJ) and had as its linker $(Gly_4Ser)_3$ SEQ ID NO: 3. Patient CJ had been treated in an earlier passive immunotherapy trial. The CJ molecule (specifically, its V region epitope or epitopes) is recognized by an anti-Id mAb named 7D11. See, also; McCormick, AA et al., Proc Natl Acad Sci USA (1999) 96:703-708).

On page 36, first full paragraph:

In an initial attempt to make a human scFv polypeptide, CJ V region genes were sequenced and cloned into a bacterial expression system using a $(Gly_4Ser)_3$ SEQ ID NO: 3 linker. Although targeted to the periplasm with a PEL-b leader, CJ scFv protein was sequestered in insoluble inclusion bodies. When mice were immunized with CJ scFv made in bacteria, no anti-CJ anti-idiotype antibody responses were detected.

On page 38 paragraphs 2, 3 and 4

The starting scFv incorporated the standard $(Gly_4Ser)_3$ SEQ ID NO: 3 linker sequence; the other scFv chains were randomly selected from the transformants obtained from the linker library cloning experiment that utilized the cloned PCR products generated from the four primers (SEQ ID NO:4-11, above). Culture supernatants from equivalent numbers of cells were electrophoresed (SDS-PAGE), and the gels were transferred to nitrocellulose membranes for Western analysis with mAb 7D11 (see above).

Some selected linker library members that were screened randomly appeared to express and accumulate as much or more CJ protein as did the CJ scFv having the conventional linker $(Gly_4Ser)_3$ SEQ ID NO: 3.

DNA of those library members expressing particularly high amounts of CJ scFv was sequenced. Results are shown in Table 2. Plasmid DNAs for selected clones were prepared and sequenced by standard methods. From the nucleotide sequences of the various CJ derived constructs, the linker sequence of individual clones was deduced. Table 2 lists some of the nucleotide and amino acid linker sequences obtained and indicates "relative expression" which means the amount of expression relative to the same protein but with the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker.

On page 39, the footnote to Table 2

* RE = Relative Expression to the $(Gly_4Ser)_3$ SEQ ID NO: 3 clone

On page 39 last paragraph:

The quantities of CJ scFv protein produced also varied (relative to the CJ scFv with the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker). This indicates that both the length and the sequence of the linker region affects the amount of protein produced by the plant cells or plants.

On page 41 last paragraph bridging to page 42:

Individual clones were sequenced, analyzed for reading frame and amino acid identity to the original CJ Ig sequence and then screened for protein expression in infected plants. Figure 1 shows the results of 9 individual CJ scFv expressing clones that demonstrated various levels of protein accumulation. Clones 20 and 30 showed high levels of expression, as well as accumulation of protein dimmers. Clone C contained a modification of the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker.

On page 42, the first full paragraph

From the sequence data, the linker sequences for individual clones were deduced. The clone numbers in Table 3 are the same as those listed in Table 2. As above, relative expression relates to the scFv protein having the $(Gly_4Ser)_3$ SEQ ID NO: 3 linker.

On page 42 , the footnote to Table 2

* RE = Relative Expression to the $(Gly_4Ser)_3$ SEQ ID NO: 3 clone